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Abstract: Associations between leisure time physical activity (LTPA) and all-cause mortality seem quite strong, however, less is known about the association of LTPA and cause-specific mortality. To examine this association data from the Third National Health and Nutrition Examination Survey (NHANES III), including 15,307 individuals of the non-institutionalized civilian United States population, were used. Data were collected from 1988 to 1994 with a mortality follow-up until 2006. LTPA was assessed during home interviews in which participants specified their LTPA and the performed frequency during the past month. Cox proportional hazards regression models were applied to analyze the risk of cause-specific mortality regarding LTPA. Hazard ratios (HRs) and 95% confidence intervals (CIs) were computed. An inverse association of LTPA with CVD mortality was observed for men and women combined for irregular (HR 0.66; 95% CI 0.51–0.85), and for regular activity (HR 0.58; 95% CI 0.47–0.72). An inverse association of LTPA with CVD mortality was observed only in women for irregular (HR 0.64; 95% CI 0.49–0.84) and for regular activity (HR 0.55; 95% CI 0.43–0.72). In men, no significant associations were seen. For mortality caused by respiratory diseases, a decreased mortality was also observed in the combined group (men and women) but after separating according to sex a decreased mortality was only observed in women. No statistically significant association of LTPA with cancer mortality was observed. Our data support an inverse association between LTPA and CVD and respiratory disease mortality in women, but not in men, and no associations with cancer.

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Sex-specific Effects of Leisure-Time Physical Activity on cause-specific Mortality in NHANES III

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Highlights

- Leisure-time physical activity (LTPA) affects disease-specific mortality
- A protective effect of LTPA on cardiovascular mortality was only seen in women
- Physical activity was inversely associated with respiratory mortality in women
- No associations between physical activity and cancer mortality was observed

Abstract

Associations between leisure time physical activity (LTPA) and all-cause mortality seem quite strong, however, less is known about the association of LTPA and cause-specific mortality. To examine this association data from the Third National Health and Nutrition Examination Survey (NHANES III), including 15,307 individuals of the non-institutionalized civilian United States population, were used. Data were collected from 1988 to 1994 with a mortality follow-up until 2006. LTPA was assessed during home interviews in which participants specified their LTPA and the performed frequency during the past month. Cox proportional hazards regression models were applied to analyze the risk of cause-specific mortality regarding LTPA. Hazard ratios (HRs) and 95% confidence intervals (CIs) were computed. An inverse association of LTPA with CVD mortality was observed for men and women combined for irregular (HR 0.66; 95% CI 0.51-0.85), and for regular activity (HR 0.58; 95% CI 0.47-0.72). An inverse association of LTPA with CVD mortality was observed only in women for irregular (HR 0.64; 95% CI 0.49-0.84) and for regular activity (HR 0.55; 95% CI 0.43-0.72). In men, no significant associations were seen. For mortality caused by respiratory diseases, a decreased mortality was also observed in the combined group (men and women) but after separating according to sex a decreased mortality was only observed in women. No statistically significant association of LTPA with cancer mortality was observed. Our data support an inverse association between LTPA and CVD and respiratory disease mortality in women, but not in men, and no associations with cancer.

Introduction

Various studies have shown the positive effects of leisure time physical activity (LTPA) on all-cause mortality (Balboa-Castillo et al., 2011; Gillum and Obisesan, 2010a, b; Haapanen-Niemi et al., 2000; Lam et al., 2004; Richard et al., 2014). Different studies also investigated specifically the association between physical activity and cause-specific mortality, for example, an association between physical activity and lower cancer mortality has been observed before (Alfano et al., 2004; Arem et al., 2014; Davey Smith et al., 2000; Kiningham, 1998; Laukkanen et al., 2011; Orsini et al., 2008; Sternfeld, 1992). A study using the data from the third National Health and Nutrition Examination Survey (NHANES III) showed a decreased risk of 48% for cancer mortality for individuals with no insulin resistance, who regularly performed vigorous physical activity (Parekh et al., 2012).

Two meta-analyses (Ibrahim and Al-Homaidh, 2011; Zhong et al., 2014), a literature review (Loprinzi et al., 2012) and other studies stated that physical activity may increase the survival of breast cancer patients (Beasley et al., 2012; Irwin et al., 2011; Peel et al., 2009), also for individuals practicing physical activity after the diagnosis (Holmes et al., 2005; Kim et al., 2013; Zhong et al., 2014). However, no increase in surviving was observed by a prospective, observational investigation (Sternfeld et al., 2009).

A more recent meta-analysis showed a mortality reduction for patients with breast or colorectal cancer patients performing physical activity before or after the diagnosis (Schmid and Leitzmann, 2014). Another meta-analysis showed a mortality reduction in colorectal cancer patients performing physical activity before or after the diagnosis (Je et al., 2013). Also for colon cancer mortality the beneficial effect of physical activity was observed (Haydon et al., 2006; Wolin et al., 2010), but no association was found for pancreatic cancer and physical activity (Lee et al., 2003). Besides the association between LTPA and cardiovascular disease (CVD) and cancer mortality (Borch et al., 2011; Hu et al., 2005; Wu et al., 2015), a strong association has been reported for LTPA and mortality due to respiratory diseases (Lam et al., 2004). For CVD mortality, e.g., meta-analyses (Nocon et al., 2008; Sluik et al., 2012) showed a risk reduction of up to 35%.

However, the strength of the associations often differed by sex and the cause of death, mostly observed in older studies. For example, Leon et. al. (1991) found an inverse relation in men between physical activity and CVD and coronary heart disease (CHD), but not for cancer mortality. Similar results were observed in other older studies (Chang-Claude and Frentzel-

Beyme, 1993; Yu et al., 2003). In 1996, an association between LTPA and cancer mortality was seen in men but not in women (Kampert et al., 1996).

To our knowledge, no associations between LTPA and digestive mortality were evaluated.

An association between LTPA and higher rates of accidental deaths was found in a study from the Netherlands (Johan de Hartog et al., 2010), where the beneficial effects from cycling were compared to the risk of higher mortality due to accidents.

In view of the huge numbers of deaths caused by cancer, CVD and respiratory diseases it seems important to have a closer look at the modifiable risk factors. Using the data of the Third National Health and Nutrition Examination Survey (NHANES III) we analyzed the association of LTPA and cause-specific mortality, such as CVD and respiratory mortality and different types of cancer mortality (colon, breast, lung and prostate) as well as cancer in general. NHANES III offers the opportunity to examine these associations in a prospective study with well-assessed outcome and a variety of potential confounders that can be taken into account in this analysis.

Methods

The NHANES III is a cross-sectional study using a complex, multistage probability design. The study participants, who all provided written informed consent, are a representative sample of the non-institutionalized civilian United States population. Participants were recruited in two phases from 1988 to 1991 and from 1991 to 1994 with a mortality follow-up until December 31 in 2006 (Diese Referenz einfügen: National Center for Health Statistics. Plan and operation of the Third National Health and Nutrition Examination Survey, 1988-94. Series 1: programs and collection procedures. *Vital Health Stat 1*. 1994; (32):1–407).

From 20,050 available participants aged between 17 and 90 years old, 3,235 participants were excluded because of missing information on waist circumference; further 1007 participants because of self-reported CVD and 492 participants because of self-reported diagnosis of cancer. After excluding further 9 participants because of insufficient mortality follow-up data, our final dataset consisted of 15,307 individuals.

Outcome variables

For the current analysis we used cause-specific mortality looking at cancer, CVD, respiratory diseases, cancer, digestive tract diseases, accidents and other death cases. Furthermore,

cancer-caused deaths were divided in different types of cancer (colon, breast, lung and prostate).

For a better understanding we have listed all categories of diseases (CVD, cancer, respiratory, digestive diseases and accidents) in detail in the appendix with the corresponding ICD-9 and ICD-10 codes.

Leisure-time physical activity

For all participants data regarding LTPA was collected during home interviews in which participants specified their LTPA (e.g. running, biking, swimming) and the performed frequency during the past month. The duration of the physical activity was not considered in NHANES III. Using the Compendium of Physical Activities (Ainsworth et al., 1993) the intensity of the physical activity was categorized in the standardized classification of metabolic equivalent (MET). One MET is specified as the metabolic rate at rest. Furthermore, physical activity was divided in moderate and vigorous intensities; moderate activities included biking, walking, running, dancing, swimming, gardening, aerobics, weight lifting, calisthenics and was defined for "other activities" by age-specific cut-offs: ≥ 3.0 METs for the age group from 20 – 39 years, ≥2.5 METs for the age group from 40 – 64 years, ≥ 2.0 METs for the age group from 65 – 79 years and ≥ 1,26 METs for the age group from ≥ 80 years. Vigorous activities included running, swimming and aerobics for all participants aged >39 years, additionally biking, dancing, gardening, and calisthenics for participants aged >64 years, and walking and weight lifting for participants aged >79 years. "Other activities" were classified as vigorous using age-specific cut-offs: ≥ 7.2 METs for the age group from 20 – 39 years, ≥6.0 METs for the age group from 40 – 64 years, ≥ 4.8 METs for the age group from 65 – 79 years and ≥ 3,00 METs for the age group ≥ 80 years (Bitte folgende Referenz einfügen: https://www.ncbi.nlm.nih.gov/pubmed/8526703).

For the analyses, three categories of LTPA were compiled: "no LTPA" for no moderate and no vigorous activity at all, "irregular LTPA" for moderate physical activity up to 4 times or vigorous activity up to 2 times per week, "regular LTPA" for more than 4 times moderate or more than 2 times vigorous physical activity per week.

Statistical analysis

Cox proportional hazards regression models were applied to compute hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of cause-specific mortality based on different physical activity behaviors. We used two models to analyze the effect of potential

confounders. Model 1 included age (continuous), sex and race/ethnicity. Model 2 included the following confounders: age (continuous), sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, others), waist circumference in cm (m: <94, w: <80; m: ≥94 & <102, w: ≥80 & <88; m: ≥102, w: ≥88), smoking status (never, former, current), duration of smoking in years, cessation of smoking in years, number of cigarettes daily, education (<high school [<12 years of education], high school [12 years of education], >high school [>12 years of education]), alcohol intake (never, <1 drink per week, ≥1 drink/week up to <1 drink per day, ≥1 drink per day), poverty income ratio (below poverty <1, above poverty ≥1), marital status (married/living together, widowed/separated/divorced, never married), diabetes, hypertension, asthma, family history of diabetes and family history of coronary disease (yes, no). In addition, all models were stratified by sex due to different sex-specific physical activity and disease patterns.

All analyses were weighted according to the NHANES III guidelines[13] to minimize sampling variability, effects of non-response, and differential selection probability (Diese Referenz einfügen: National Center for Health Statistics. Plan and operation of the Third National Health and Nutrition Examination Survey, 1988-94. Series 1: programs and collection procedures. *Vital Health Stat 1*. 1994; (32):1–407). All analyses were computed using STATA 13.1 (Stata Corporation, College Station, TX, USA).

Results

Characteristics of the 15,307 participants are shown in table 1. More current smokers were observed in the group of no LTPA (men: 44.5%, women: 29.8%) than in the regular LTPA group (men: 30.1%, women: 22.0%). Participants below poverty reported to practice less LTPA. Men and women with a higher education practiced much more irregular and regular LTPA compared to participants with a lower education (less than high school). During the time of the follow-up (mean 158 person-months), 2,864 participants died; of these 648 died of cancer, 1,150 of CVD, 286 of respiratory diseases, 141 of accidents, 53 of digestive diseases and 586 of other causes of death. The cancer group can be divided in the different types of cancer: 62 participants died of colon cancer, 43 of breast cancer, 193 of lung cancer and 53 men of prostate cancer.

Cancer mortality

No statistically significant association of LTPA with cancer mortality was observed (Table 2). By dividing the cancer group in subgroups of colon, breast, lung and prostate cancer, no

significant results were found except for men with lung cancer in the age-, sex- and race-adjusted model (HR 0.36; 95% CI 0.17-0.76, Table 3).

CVD mortality

An inverse association of LTPA with CVD mortality was found in the combined model (men and women) for irregular physical activity (HR 0.66; 95% CI 0.51-0.85), and for regular activity (HR 0.58; 95% CI 0.47-0.72), both age- and race-adjusted (Table 2). After multivariable adjustment the effects were reduced only minimally resulting in a HR of 0.71 (95% CI 0.56-0.90) for irregular activity and HR 0.70 (95% CI 0.57-0.86) for regular activity. Separating the participants according to sex the situation looks a little different:

In women an inverse association of LTPA with CVD mortality was found for irregular physical activity (HR 0.64; 95% CI 0.49-0.84), and for regular activity (HR 0.55; 95% CI 0.43-0.72), both age- and race-adjusted. After multivariable adjustment the effects were reduced only minimally resulting in a HR of 0.67 (95% CI 0.50-0.89) for irregular activity and HR 0.65 (95% CI 0.50-0.83) for regular activity.

In men, the results tend to go in the same direction as in women but no significant association was found for irregular activity, neither in the age- and race- adjusted model, nor in the multivariable adjustment model. The significant association of regular LTPA with mortality in the age- and race adjusted model (HR 0.65; 0.44-0.98) was attenuated and no longer statistically significant after multivariable adjustment. The reason for the insignificant results could be small number of deaths in the group of no LTPA.

Respiratory diseases mortality

For mortality caused by respiratory diseases, similar results as in CVD mortality were observed. An inverse association of LTPA with respiratory disease mortality was found in the combined model (men and women) for irregular physical activity (HR 0.37; 95% CI 0.23-0.59), and for regular activity (HR 0.32; 95% CI 0.22-0.47), both age- and race-adjusted (Table 2). After multivariable adjustment the effects were reduced only minimally resulting in a HR of 0.45 (95% CI 0.26-0.75) for irregular activity and HR 0.43 (95% CI 0.29-0.64) for regular activity. Separating the participants according to sex the situation looks different:

A decreased mortality was observed in women in the age- and race-adjusted model for irregular activity with a HR of 0.27 (95% CI 0.14-0.51), and regular activity with a HR of

0.27 (95% CI 0.17-0.44). By multivariable adjustment, the effect was similar (HR 0.30; 95% CI 0.14-0.66) for irregular activity and for regular activity (HR 0.36; 95% CI 0.22-0.58).

In men, the results tend to go in the same direction as in women but no association was observed for men with irregular LTPA, but for regular LTPA in the age- and race-adjusted model (HR 0.43; 95% CI 0.22-0.86). This result did not remain statistically significant after multivariable adjustment.

Digestive mortality, accidents and other

No significant results were found for deaths due to digestive diseases or accidents; however, it has to be mentioned that the case numbers were extremely small. For other causes of death, significant results were observed in men with irregular and regular LTPA in the age- and race adjusted model as well as in the multivariable adjusted model (HR 0.53; 95% CI 0.30-0.93, HR 0.57; 95% CI 0.36-0.89, respectively). For women results were only significant for regular LTPA in the age- and race-adjusted model (Table 2).

Discussion

In this study LTPA was associated with lower CVD and respiratory diseases mortality in women. Associations in men were rather weak; indeed an association was only seen when adjusting for age, sex and race but not in the multivariable-adjusted model. For cancer, no mortality reduction was found in participants performing LTPA. Analyzing the different types of cancer (colon, breast, lung and prostate cancer), we observed an association in men with lung cancer in the age, sex and race adjusted model. LTPA was also associated with other causes of death.

In line with this study, the association of physical activity, in particular, but not exclusively LTPA, and cause-specific mortality was observed previously (Alfano et al., 2004; Arem et al., 2014; Borch et al., 2011; Davey Smith et al., 2000; Hu et al., 2005; Ibrahim and Al-Homaidh, 2011; Je et al., 2013; Kiningham, 1998; Lam et al., 2004; Laukkanen et al., 2011; Loprinzi et al., 2012; Nocon et al., 2008; Orsini et al., 2008; Schmid and Leitzmann, 2014; Sluik et al., 2012; Sternfeld, 1992; Wu et al., 2015; Zhong et al., 2014). In the study by Lam et al. (2004), not only a risk reduction for CVD, cancer and respiratory diseases mortality for physically active participants was observed, but it was also estimated that 20% of all 31,349 registered deaths in 1998 in Hong Kong were assignable to physical inactivity in participants aged over

35 years. A prospective cohort study from London pointed out that men with faster walking paces had a lower risk of death from coronary heart diseases, from other CVD and from cancer, namely colorectal and hematopoietic cancers (Davey Smith et al., 2000). Moreover, a comparatively small daily amount of 10 to 36 minutes of LTPA of moderate intensity was associated with a mortality risk reduction for premature death especially regarding coronary heart diseases in middle-aged and older men with high risk factors for coronary heart diseases (Leon et al., 1997). Another study recently showed that LTPA practiced 150 minutes or more per week was linked with a 28 % lower CVD mortality risk (Gunnell et al., 2014). In general, especially for CVD mortality, many studies have been published (Hu et al., 2013; Leon and Connett, 1991; Leon et al., 1997; Slattery et al., 1989; Sone et al., 2013). The listed studies all support our own results, showing that even though in our findings the association of LTPA and CVD and respiratory diseases mortality was rather weak in men (but not in women), LTPA seems to be a protective modifiable survival factor.

In 2001, an analysis of the Nurses' Health Study (only women were included) found inverse associations between physical activity and CVD, cancer and respiratory diseases. Interestingly, the strongest inverse association for physical activity for cause-specific mortality was found for respiratory diseases (Rockhill et al., 2001).

While there is strong evidence for a protective effect of physical activity on the circulatory system (Physical Activity Guidelines Advisory Committee, 2008), the situation with cancer is more complex; associations between LTPA and cancer mortality seem to vary: According to the report of the World Cancer Research Fund and Physical Activity Guidelines Advisory Committee (2009) from the US, there is strong evidence for an inverse association between LTPA and colon and breast cancer, but only moderate evidence for an association between LTPA and lung, ovarian and endometrial cancers. A meta-analysis imbedding six studies with a total of 12,108 breast cancer patients estimated a risk reduction in breast cancer mortality for women with a BMI of <25 kg/m^2 who performed physical activity before diagnosis. Breast cancer mortality was reduced by 34% in women practicing physical activity after the diagnoses (Ibrahim and Al-Homaidh, 2011). A more recent meta-analysis showed a risk reduction in breast cancer mortality for women who performed any amount of physical activity before the diagnosis (Zhong et al., 2014). In our study we observed no associations but we had only a limited number of 43 death cases.

A risk reduction for colon cancer mortality has been shown for constant high physical activity over 10 years compared to people with constant low physical activity (Wolin et al., 2010).

This result is emphasized by a meta-analysis reporting a mortality risk reduction for colorectal cancers for participants performing physical activity before or after the diagnosis (Je et al., 2013). In 2011 a study reported that men who practiced vigorous physical activity 3 hours or more per week had a 61% reduced mortality risk for prostate cancer (Kenfield et al., 2011).

A possible explanation for the significant results in other causes of death might be an influence of LTPA on neurological diseases because one study observed a risk reduction for death due to Alzheimer disease for participants performing LTPA (Scarmeas et al., 2011). However, further research in this direction is warranted.

We did not find any associations for LTPA and digestive mortality in our study and also no sources neither with positive nor negative results in the literature. However, as LTPA seems to be a factor with a strong impact on many diseases, it cannot be excluded that an association may be observed in future studies focusing on digestive diseases.

In contrast to a study from 2010 that observed higher mortality due to accidents in participants performing LTPA (Johan de Hartog et al., 2010), we did not observe such an association.

Strengths and limitations

A couple of strengths of this study can be mentioned. The data of NHANES III with a long follow-up period of 18 years has a large sample size of 15,307 participants and is representative for the non-institutionalized US population. Furthermore, many different confounders were considered in the statistical analyses. Only a few studies had these advantages before, which gives us the chance to get a reliable view on the association of LTPA and cause-specific mortality. Still it might be that unknown or unmeasured confounders may have been missed. Another limitation might be a family history of cancer, which was not assessed in NHANES. Furthermore, recall and misclassification bias may have occurred. Additionally, LTPA was self-reported and no information about the duration of LTPA was collected. Also data about LTPA were assessed at baseline but not at follow up, so potential changes were not considered. Also, in NHANES III only frequency per week, but not duration of physical activity was assessed. Thus, LTPA of participants with "irregular" physical activity who engage in long bouts may be underestimated and vice versa. Tämer, kannst du hier einen (oder zwei) Sätze schreiben, ob die Ergebnisse, die das auch so gemacht haben, grundsätzlich andere Ergebnisse zeigen, als Studien die Dauer und Intensität einbeziehen. Another large limitation is that functional ability are not considered. We tried to capture an individual’s ability to perform moderate or vigorous physical activity by using

different age cut-points.

A further limitation is the small numbers of deaths for the different types of cancer. Thus, further research with a longer mortality follow-up would be worthwhile.

Conclusions

Regular and irregular physical activity was inversely associated with CVD in the combined model (men and women). Separated by sex regular and irregular physical activity was inversely associated with CVD mortality only in women, but not in men. For mortality caused by respiratory diseases similar inverse results in the combined model (men and women) and in women were observed, which is in line with most published studies. In view of the huge numbers of deaths caused by cancer, CVD and respiratory diseases it is important to have a closer look at the modifiable risk factors to achieve a reduction of the death rates of the diseases.

Conflicts of Interest

None.

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None

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Table 1

Baseline characteristics by sex and leisure-time physical activity (LTPA), NHANES III, 1988-1994

Characteristics[1]	*Males* No LTPA (n=1032)	*Males* irregular LTPA (n=2497)	*Males* regular LTPA (n=3617)	*Females* No LTPA (n=2028)	*Females* irregular LTPA (n=3158)	*Females* regular LTPA (n=2975)
Proportion (%)	9.4	36.6	54.0	16.8	41.1	42.1
Age at baseline, mean (SE)	42.6 (0.7)	39.7 (0.4)	40.2 (0.6)	46.1 (0.6)	39.2 (0.5)	43.0 (0.7)
Race/ethnicity, %						
Non-hispanic white	61.1	76.5	76.9	59.3	76.4	79.0
Non-Hispanic black	12.6	9.3	11.1	18	11.3	10.0
Mexican-American	13.4	6.1	4.8	9.3	5.0	3.5
Other race/ethnicity	13.0	8.0	7.2	13.3	7.3	7.5
Waist circumference (cm), mean (SE)	94.6 (1.1)	95.8 (0.5)	92.6 (0.4)	92.7 (0.9)	88.1 (0.5)	85.4 (0.4)
Smoking status, %						
Never	32.2	30.4	38.4	53.0	56.5	57.6
Former	23.2	29.5	31.5	17.1	16.3	20.4
Current	44.5	40.1	30.1	29.8	27.2	22.0
Years of smoking, mean (SE)	25.5 (0.9)	21.0 (0.5)	21.0 (0.5)	23.2 (0.8)	18.4 (0.4)	18.9 (0.6)
Years since cessation of smoking, mean (SE)	13.3 (1.0)	11.8 (0.6)	14.2 (0.6)	12.1 (1.0)	9.5 (0.6)	12.5 (1.0)
Number of daily consumption of cigarettes, mean (SE)	21.2 (1.0)	22.0 (0.6)	19.0 (0.6)	18.4 (0.8)	17.5 (0.5)	15.8 (0.6)
Alcohol intake, %						
never consumer	42.3	33.5	32.5	71.8	50.5	47.1
<=1 drink/week	25.8	24.7	23.2	17.1	29.4	28.3
1 drink /week to < 1 drink/day	25.4	30.3	33.0	8.3	17.2	20.1
>=1drink/day	6.5	11.5	11.3	2.7	2.9	4.5
Poverty income ratio: below poverty, %	17.1	9.2	10.2	24.0	13.1	10.1
Education, %						
< high school	44.6	26.3	22.6	41.7	23.0	17.6
High school	34.2	34.1	28.3	37.8	39.4	34.0
> high school	21.2	39.6	49.1	20.5	37.6	48.5
Marital status, %						

married/living together	65.8	71.7	62.8	56.3	61.6	59.2
widowed/separated/divorced	13.9	6.9	9.8	28.7	18.3	21.3
never married	20.4	21.4	27.4	14.9	20.1	19.6
History of hypertension, %	18.6	21.0	17.7	29.8	20.0	19.0
History of diabetes, %	4.0	4.3	2.9	8.1	4.8	3.2
History of Asthma, %	9.2	7.0	7.0	7.4	7.9	8.1
Family history of diabetes, %	33.4	38.9	38.0	51.1	51.6	46.7
Family history of coronary disease, %	12.0	16.4	14.4	15.3	19.3	18.3

[1]Values are unadjusted and weighted except n

Table 2

Association between leisure time physical activity (LTPA) and cause-specific mortality, NHANES III, 1988-1994

	No LTPA		**Irregular LTPA**			**Regular LTPA**			
				Model 1	**Model 2**		**Model 1**	**Model 2**	**p-interaction***
	No. of deaths **	Hazard Ratio	No. of deaths	Hazard Ratio	Hazard Ratio	No. of deaths	Hazard Ratio	Hazard Ratio	
	Cancer								
Total	147	1.00	201	0.94 (0.63-1.39)	1.06 (0.71-1.58)	300	0.81 (0.57-1.17)	1.04 (0.71-1.52)	
men	58	1.00	107	0.71 (0.39-1.28)	0.88 (0.50-1.55)	202	0.67 (0.41-1.12)	0.94 (0.57-1.52)	
women	89	1.00	94	1.05 (0.69-1.61)	1.17 (0.78-1.77)	98	0.83 (0.52-1.32)	1.01 (0.61-1.67)	0.979
	CVD								
Total	362	1.00	304	0.66 (0.51-0.85)	0.71 (0.56-0.90)	484	0.58 (0.47-0.72)	0.70 (0.57-0.86)	
men	124	1.00	165	0.72 (0.44-1.17)	0.80 (0.51-1.26)	303	0.65 (0.44-0.98)	0.81 (0.53-1.22)	
women	238	1.00	139	0.64 (0.49-0.84)	0.67 (0.50-0.89)	181	0.55 (0.43-0.72)	0.65 (0.50-0.83)	0.670
	Respiratory diseases								
Total	100	1.00	74	0.37 (0.23-0.59)	0.45 (0.26-0.75)	112	0.32 (0.22-0.47)	0.43 (0.29-0.64)	
men	39	1.00	47	0.58 (0.28-1.20)	0.81 (0.37-1.77)	71	0.43 (0.22-0.86)	0.63 (0.31-1.29)	
women	61	1.00	27	0.27 (0.14-0.51)	0.30 (0.14-0.66)	41	0.27 (0.17-0.44)	0.36 (0.22-0.58)	0.188
	Accidents								
Total	29	1.00	39	0.62 (0.28-1.35)	0.71 (0.32-1.58)	73	0.91 (0.49-1.69)	1.16 (0.62-2.19)	
men	18	1.00	25	0.47 (0.16-1.37)	0.53 (0.18-1.55)	56	0.78 (0.36-1.70)	1.06 (0.48-2.34)	
women	11	1.00	14	1.00 (0.38-2.59)	1.12 (0.39-3.25)	17	1.13 (0.47-2.68)	1.28 (0.56-2.93)	0.733
	Digestive diseases								
Total	16	1.00	18	0.68 (0.17-2.65)	0.95 (0.20-4.47)	19	0.98 (0.29-3.36)	1.36 (0.39-4.73)	
men	10	1.00	8	0.38 (0.07-2.04)	0.54 (0.14-2.09)	12	0.74 (0.14-3.89)	1.00 (0.25-3.97)	
women	6	1.00	10	1.43 (0.23-8.81)	2.22 (0.21-23.62)	7	1.31 (0.26-6.52)	1.57 (0.31-8.00)	0.753
	Other causes of death								
Total	170	1.00	173	0.59 (0.42-0.83)	0.68 (0.48-0.95)	243	0.52 (0.37-0.72)	0.68 (0.47-0.98)	
men	70	1.00	92	0.43 (0.25-0.76)	0.53 (0.30-0.93)	141	0.43 (0.29-0.65)	0.57 (0.36-0.89)	
women	100	1.00	81	0.77 (0.52-1.15)	0.84 (0.56-1.26)	102	0.59 (0.36-0.95)	0.77 (0.45-1.31)	0.398

Model 1: age, sex and race adjusted (for the separate sexes analysis sex is not a confounder, so it is age and race adjusted)

Model 2 (16 confounders): age, sex, race, waist circumference, smoking status, duration of smoking in years, cessation of smoking in years, number of cigarettes daily, education, poverty income ratio, marital status, diabetes, hypertension, asthma, family history of diabetes and family history of coronary disease

* interaction term sex * physical activity

**non-weighted

Table 3

Association of leisure time physical activity (LTPA) and different cancer type mortality, NHANES III, 1988-1994

	No LTPA		**Irregular LTPA**			**Regular LTPA**			
				Model 1	**Model 2**		**Model 1**	**Model 2**	**p-interaction***
	No. of deaths**	Hazard Ratio	No. of deaths	Hazard Ratio	Hazard Ratio	No. of deaths	Hazard Ratio	Hazard Ratio	
	Colon Cancer								
Total	13	1.00	14	0.89 (0.36-2.19)	0.96 (0.37-2.49)	35	0.99 (0.51-1.90)	1.21 (0.60-2.45)	
men	6	1.00	8	0.62 (0.17-2.29)	0.64 (0.16-2.60)	26	0.84 (0.32-2.23)	0.90 (0.35-2.30)	
women	7	1.00	6	1.13 (0.30-4.29)	1.13 (0.28-4.69)	9	0.94 (0.27-3.26)	1.19 (0.38-3.71)	0.945
	Breast Cancer								
women	17	1.00	12	0.98 (0.36-2.70)	0.98 (0.33-2.93)	13	0.98 (0.31-3.11)	1.18 (0.34-4.03)	-
	Lung Cancer								
Total	47	1.00	68	0.91 (0.50-1.66)	1.15 (0.66-2.00)	78	0.64 (0.36-1.14)	0.93 (0.54-1.62)	
men	26	1.00	40	0.55 (0.22-1.34)	0.73 (0.33-1.59)	54	0.36 (0.17-0.76)	0.56 (0.27-1.17)	
women	21	1.00	28	1.47 (0.75-2.88)	1.79 (1.01-3.15)	24	1.17 (0.56-2.44)	1.56 (0.72-3.41)	0.054
	Prostate Cancer								
men	5	1.00	19	1.05 (0.27-4.01)	1.23 (0.28-5.43)	29	0.58 (0.16-2.12)	0.70 (0.19-2.57)	

Model 1: age, sex and race adjusted (for the separate sexes analysis sex is not a confounder, so it is age and race adjusted)
Model 2 (16 confounders): age, sex, race, waist circumference, smoking status, duration of smoking in years, cessation of smoking in years, number of cigarettes daily, education, poverty income ratio, marital status, diabetes, hypertension, asthma, family history of diabetes and family history of coronary disease

* interaction term sex * physical activity

**non-weighted

Appendix

For a better understanding we have listed all diseases for the categories of CVD, cancer, respiratory, digestive diseases and accidents that we used below coded with ICD-9 and ICD-10.

CVD was assessed as follows: Major cardiovascular diseases (I00-I78), diseases of heart (I00-I09,I11,I13,I20-I51), acute rheumatic fever and chronic rheumatic heart diseases (I00-I09), hypertensive heart disease (I11), hypertensive heart and renal disease (I13), ischemic heart diseases (I20-I25), acute myocardial infarction (I21-I22), other acute ischemic heart diseases (I24), other forms of chronic ischemic heart disease (I20,I25), atherosclerotic cardiovascular disease, so described (I25.0), all other forms of chronic ischemic heart disease (I20,I25.1-I25.9), other heart diseases (I26-I51), acute and subacute endocarditis (I33), diseases of pericardium and acute myocarditis (I30-I31,I40), heart failure (I50), all other forms of heart disease (I26-I28,I34-I38,I42-I49,I51), essential (primary) hypertension and hypertensive renal disease (I10,I12), cerebrovascular diseases (I60-I69), atherosclerosis (I70), other diseases of circulatory system (I71-I78), aortic aneurysm and dissection (I71), other diseases of arteries, arterioles and capillaries (I72-I78), other disorders of circulatory system (I80-I99)

Cancer: Malignant neoplasms (C00-C97): malignant neoplasms of lip, oral cavity and pharynx (C00-C14), malignant neoplasm of esophagus (C15), malignant neoplasm of stomach (C16), malignant neoplasms of colon, rectum and anus (C18-C21), malignant neoplasms of liver and intrahepatic bile ducts (C22), malignant neoplasm of pancreas (C25), malignant neoplasm of larynx (C32), malignant neoplasms of trachea, bronchus and lung (C33-C34), malignant melanoma of skin (C43), malignant neoplasm of breast (C50), malignant neoplasm of cervix uteri (C53), malignant neoplasms of corpus uteri and uterus, part unspecified (C54-C55), malignant neoplasm of ovary (C56), malignant neoplasm of prostate (C61), malignant neoplasms of kidney and renal pelvis (C64-C65), malignant neoplasm of bladder (C67), malignant neoplasms of meninges, brain and other parts of central nervous system (C70-C72), malignant neoplasms of lymphoid, hematopoietic and related tissue (C81-C96), Hodgkin's disease (C81), non-Hodgkin's lymphoma (C82-C85), leukemia (C91-C95), multiple myeloma and immunoproliferative neoplasms (C88,C90), other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue (C96), all other and unspecified malignant neoplasms (C17,C23-C24,C26-C31,C37-C41, C44-C49,C51-C52,C57-C60,C62-C63,C66,C68-C69,C73-C80,C97)

Respiratory: Influenza and pneumonia (J10-J18), influenza (J10-J11), Pneumonia (J12-J18), other acute lower respiratory infections (J20-J22), acute bronchitis and bronchiolitis (J20-J21), unspecified acute lower respiratory infection (J22), chronic lower respiratory diseases (J40-J47), bronchitis, chronic and unspecified (J40-J42), emphysema (J43), asthma (J45-J46), other chronic lower respiratory diseases (J44,J47), pneumoconioses and chemical effects (J60-J66,J68), pneumonitis due to solids and liquids (J69), other diseases of respiratory system (J00-J06,J30-J39,J67,J70-J98)

Digestive tract diseases: Peptic ulcer (K25-K28), diseases of appendix (K35-K38), hernia (K40-K46), chronic liver disease and cirrhosis (K70,K73-K74), alcoholic liver disease (K70), other chronic liver disease and cirrhosis (K73-K74), cholelithiasis and other disorders of gallbladder (K80-K82)

Accidents: Accidents (unintentional injuries) (V01-X59,Y85-Y86), transport accidents (V01-V99,Y85), motor vehicle accidents (V02-V04,V09.0,V09.2,V12-V14,V19.0-V19.2, V19.4-V19.6,V20-V79,V80.3-V80.5,V81.0-V81.1,V82.0-V82.1,V83-V86, V87.0-V87.8,V88.0 V88.8,V89.0,V89.2), other land transport accidents (V01,V05-V06,V09.1,V09.3-V09.9, V10-V11, V15-V18,V19.3,V19.8-V19.9,V80.0-V80.2,V80.6-V80.9,V81.2-V81.9, V82.2-V82.9,V87.9,V88.9,V89.1,V89.3,V89.9), water, air and space, and other and unspecified transport accidents and their sequelae (V90-V99,Y85), nontransport accidents (W00-X59,Y86), falls (W00-W19), accidental discharge of firearms (W32-W34), accidental drowning and submersion (W65-W74), accidental exposure to smoke, fire and flames (X00-X09), accidental poisoning and exposure to noxious substances (X40-X49), other and unspecified nontransport accidents and their sequelae (W20-W31,W35-W64,W75-W99,X10-X39,X50-X59,Y86), intentional self-harm (suicide) (*U03,X60-X84,Y87.0), intentional self-harm (suicide) by discharge of firearms (X72-X74), intentional self-harm (suicide) by other and unspecified means and their sequelae (*U03,X60-X71,X75-X84,Y87.0), assault (homicide) (*U01-*U02,X85-Y09,Y87.1), assault (homicide) by discharge of firearms (*U01.4,X93-X95), assault (homicide) by other and unspecified means and their sequelae (*U01.0-*U01.3,*U01.5-*U01.9,*U02,X85-X92,X96-Y09,Y87.1), legal intervention (Y35,Y89.0), events of undetermined intent (Y10-Y34,Y87.2,Y89.9), discharge of firearms, undetermined intent (Y22-Y24), other and unspecified events of undetermined intent and their sequelae (Y10-Y21,Y25-Y34,Y87.2,Y89.9), operations of war and their sequelae (Y36,Y89.1), complications of medical and surgical care (Y40-Y84,Y88).